Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1964, **30**, 763-768

A Controlled Trial of Live-Virus Vaccine against Measles in Chile*

CONRADO RISTORI, M.D., M.P.H.,[1] HORACIO BOCCARDO, M.D.,[2] M.P.H., MARIO MIRANDA, M.D., M.P.H.[2] & MANUEL BORGOÑO, M.D., M.P.H.[2]

In view of the high mortality from measles in Chile, it was decided to undertake a double-blind, controlled trial of the Enders Edmonston B strain of live measles vaccine in that country as part of a WHO-sponsored programme to obtain information on reactions to that vaccine strain and on the antibody response elicited in children.

Between July and December 1962, some 530 children 8 months to 3 years old received inoculations of vaccine, with or without gamma-globulin, or were given a placebo injection. The reactions were generally of moderate intensity and were not appreciably reduced in either frequency or intensity by gamma-globulin. Serological conversion was achieved in about 90% of the vaccinated.

On the basis of this experience, it was decided to institute a large-scale immunization in Chile with the same vaccine; the campaign began in May 1963.

Acute infectious diseases constitute an important problem in Chile; and prominent among them is measles, which was responsible for 2116 deaths (50.9% of all deaths from acute infectious diseases) in 1960 and for 1822 deaths (46.5%) in 1961 (Chile, Servicio de Salud, 1961; Ristori et al., 1962). The 1960 measles mortality represented 2.3% of deaths from all causes, and some 42% of measles deaths in that year occurred in children under one year of age and 52% in those 1-4 years old. Deaths from this disease show an inverse correlation not only to increasing age but also to better socio-economic conditions and are about four times as numerous in the south as in the north of Chile.

In view of this situation the Chilean National Health Service has followed with interest the development of procedures for conferring immunity to measles.

In November 1961 the World Health Organization sought the advice of a group of experts regarding measles vaccination, and it was agreed, *inter alia*, that the Enders vaccine prepared from live virus of the Edmonston B strain should be used in simultaneous trials in different countries with a view to determining (*a*) its innocuity by observation of the reactions to which it might give rise when administered either alone or with gamma-globulin and (*b*) its efficacy as shown by the antibody response elicited.

Chile agreed to serve as one of the countries selected for these trials, which were planned in collaboration with WHO. The necessary vaccine[3] and diluent, gamma-globulin, syringes, needles and data-recording forms were supplied through WHO.

ORGANIZATION OF THE TRIAL

The study was carried out between July and December 1962 among children in institutions and in their own homes. Two paediatricians, eight nurses and eleven senior students from the National Health Service School of Nursing took part in collaboration with public health specialists from the Department of Health Protection.

* The field team conducting the trial included, in addition to the authors, the following nurses from the Department of Health Protection: Silvia Muñoz, Blanca Carillo, Fresia Concha, Irene Assael and Luisa Sanchez; the following nursing instructors from the National Health Service School of Nursing: Irma Olivari, Marta Aravena and Susana Burton; and eleven fourth-year students from the School of Nursing.

[1] Chief, Department of Health Protection, National Health Service, Santiago, Chile.

[2] Epidemiology Section, National Health Service, Santiago, Chile.

[3] Kindly made available by Dr M. R. Hilleman of the Merck Institute for Therapeutic Research, West Point, Pa., USA.

Selection of children

A total of 530 children, eight months to three years of age, were chosen for vaccination, any children with a clear history of measles being excluded. Children suffering from malnutrition or coming from poor homes were included; for them, as for all the others, a note was made at the moment of inoculation of their nutritional state, weight, height and temperature.

Immunization

The children were divided at random into five groups, each of about 100. Group I received live vaccine alone; Group II, vaccine plus 0.01 ml of gamma-globulin per pound of body-weight; Group III, vaccine plus 0.005 ml of gamma-globulin per pound of body-weight; Group IV, vaccine plus 0.0025 ml of gamma-globulin per pound of body-weight; and Group V (the control group), a placebo injection of sterile tissue-culture medium.

The live lyophilized vaccine was received, ready for dilution, in vials containing four doses each. The diluent (distilled water free of any preservative) was received with the vaccine. After rehydration, the vaccine was injected subcutaneously into the left arm in a dose of 0.25 ml (2500 $TCID_{50}$) to all children of Groups I-IV. Gamma-globulin was administered subcutaneously into the right arm, immediately after the vaccine, to children of Groups II, III and IV. The placebo, in a dose of 0.25 ml, was injected into the left arm of children of Group V.

Comparability of vaccination groups

Tables 1 and 2 show the sex and age distribution of the trial population by vaccination group. It will be seen that there are only minor differences between the various groups. It is apparent from Table 3 that the nutritional state of some 92% of the children was satisfactory. The 43 undernourished children constitute too small a group to allow of valid conclusions, but there seemed to be no important differences between the well and the poorly nourished so far as the results of vaccination are concerned.

Follow-up

As one of the principal objectives of this study was to determine the reactions caused by the different vaccination schedules, arrangements were made to observe the children daily for at least 21 days; in most cases, indeed, they were followed up for about 30 days. In order to ensure unbiased observation and recording, the observers were not told which group any child had been assigned.

TABLE 1
SEX DISTRIBUTION BY VACCINATION GROUP

Group	Male		Female	
	No.	%	No.	%
I	57	52.3	52	47.7
II	56	51.0	54	49.0
III	57	51.8	53	48.2
IV	48	44.4	60	55.6
V	45	48.4	48	51.6
Total	263	49.6	267	50.4

TABLE 2
AGE DISTRIBUTION BY VACCINATION GROUP

Age-group	Group I		Group II		Group III		Group IV		Group V		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
8 months-1 year	24	22.0	28	25.5	29	26.4	29	26.9	25	26.9	135	25.5
1 year-2 years	53	48.6	54	49.1	53	48.2	53	49.1	53	57.0	266	50.2
2 years-3 years	32	29.4	28	25.5	28	25.4	26	24.1	15	16.1	129	24.3
Total	109	100	110	100	110	100	108	100	93	100	530	100

TABLE 3
NUTRITIONAL STATE BY VACCINATION GROUP

Group	Good		Poor	
	No.	%	No.	%
I	100	91.7	9	8.3
II	100	90.9	10	9.1
III	102	92.7	8	7.3
IV	102	94.4	6	5.6
V	83	89.2	10	10.8
Total	487	91.9	43	8.1

Serological investigation

A 6-8-ml blood sample was taken from every child immediately before vaccination and a second at the end of the observation period (21-32 days later). The blood was centrifuged and kept in special refrigerated containers until it was examined. The examinations were performed in two laboratories—one in Chile, the other in South Africa. The results reported below are those from the Chilean laboratory.

RESULTS

Temperature

Some 25.7% of children in Group I had a maximum rectal temperature greater than 39°C (Table 4). At lower temperatures there were no symptoms that could be related to fever. Gamma-globulin did not significantly modify the temperature.

One child's temperature rose to 40°C and he had convulsions of short duration; this child was in Group II and had received the maximum dose of gamma-globulin.

A few instances of high temperature were observed in the control group; these were all due to intercurrent diseases. Two cases of typical measles were seen in this group a few days after the beginning of the follow-up; one case of scarlet fever was also observed among the controls.

Febrile reactions among those receiving vaccine occurred on or after the fifth day and lasted between 3.5 days for Group IV and a little over 5 days for Group I.

Rash

Over 39% of the children in Group I had no rash; some 23% had a few scattered spots; and a little over 37% had a diffuse but mild rash (Table 5). The proportions suffering from rash in the groups receiving gamma-globulin as well as vaccine were not greatly different from those in Group I. In Group V, which received only the placebo, three children had a generalized rash: the two suffering from measles and the child with scarlet fever.

Other symptoms

The analysis of other symptoms observed (Table 6) clearly demonstrates the high frequency with which Chilean children suffer from upper respiratory disorders—especially coryza, cough and pharyngitis—towards the end of winter and in spring. Conjunctivitis, diarrhoea and enanthema were seen considerably more frequently among the four groups that received vaccine than among the controls. Seven children had Koplik's spots, three of them in Group I.

TABLE 4
MAXIMUM RECORDED RECTAL TEMPERATURES AND TIMES OF ONSET AND DURATION OF FEVER BY VACCINATION GROUP

Group	Total children in group	Maximum rectal temperature								Average time to onset of fever (days)	Average duration of fever (days)
		< 37°C		37°C-38°C		38.1°C-39°C		≥ 39.1°C			
		No.	%	No.	%	No.	%	No.	%		
I	109	22	20.2	17	15.6	42	38.5	28	25.7	5.5	5.1
II	110	29	26.4	24	21.8	35	31.8	22	20.0	6.5	3.9
III	110	30	27.3	24	21.8	40	36.4	16	14.5	5.6	4.2
IV	108	30	27.8	27	25.0	25	23.1	26	24.1	6.9	3.5
V	93	65	70.0	17	18.3	7	7.5	4	4.3	2.8	7.4

TABLE 5
OCCURRENCE OF RECORDED RASH AND TIME OF ONSET AND DURATION OF RASH BY VACCINATION GROUP

Group	No rash		Localized rash		Generalized rash		Average time to onset of rash (days)	Average duration of rash (days)
	No.	%	No.	%	No.	%		
I	43	39.4	25	22.9	41	37.6	8.8	4.5
II	57	51.8	27	24.5	26	23.6	8.4	4.5
III	58	52.7	32	29.1	20	18.2	8.2	5.2
IV	45	41.7	40	37.0	23	21.3	8.8	4.1
V	85	91.4	5	5.4	3	3.2	10.4	4.5

TABLE 6
OTHER SYMPTOMS OBSERVED

Symptoms	Group I		Group II		Group III		Group IV		Group V	
	No.	%	No.	%	No.	%	No.	%	No.	%
Coryza	99	90.8	97	88.2	91	82.7	91	84.3	73	78.5
Cough	90	82.6	89	80.9	76	69.1	82	75.9	50	53.8
Pharyngitis	88	80.7	79	71.8	63	57.3	79	73.1	27	29.0
Enanthema	29	26.6	29	26.4	28	25.5	28	25.9	1	1.1
Koplik's spots	3	2.8	1	0.9	1	0.9	2	1.9	—	—
Conjunctivitis	51	46.8	40	36.4	35	31.8	39	36.1	8	8.6
Diarrhoea	37	33.9	42	38.2	30	27.3	49	45.4	13	14.0
Convulsions	—	—	1	0.9	—	—	—	—	—	—
No symptoms	1	0.9	2	1.8	6	5.5	3	2.8	17	18.3

Epidemiological investigation

Six months after the completion of the observation phase, 100 children who had received the vaccine only (Group I) and 85 who had had the placebo (Group V) were revisited to determine whether any of them had had measles during the interval, only cases occurring more than two weeks after inoculation being considered. This additional investigation was not planned in the original programme but was prompted by the fact that a measles epidemic occurred in Santiago.

The results clearly demonstrate the efficacy of the vaccine: no cases at all occurred in the vaccine group, whereas 14 cases of measles, with one death, had occurred among the unvaccinated controls.

Serological investigation

The results of the complement-fixation tests performed at the Bacteriological Institute, Santiago, on the prevaccination sera and on sera drawn at the end of the observation period are shown in Table 7. It will be seen that good serological conversion from negative to positive took place in most children in Groups I-IV, but that no conversions took place in the control group.

DISCUSSION

This study shows that vaccination against measles with a subcutaneous dose of 2500 $TCID_{50}$ of the live, attenuated Edmonston B strain produces a

TABLE 7

RESULTS OF COMPLEMENT-FIXATION TESTS

Group	Blood sample [a]	No. of negative sera	No. of positive sera [b]				Total
			1 : 64	1 : 128	1 : 256	1 : 512	
I	1st	17	1	1	—	—	19
	2nd	1	2	16	—	—	
II	1st	17	1	—	—	—	18
	2nd	1	1	16	—	—	
III	1st	23	—	—	—	—	23
	2nd	1	3	3	12	4	
IV	1st	12	—	—	—	—	12
	2nd	2	—	1	7	2	
V	1st	15	—	1	—	—	15
	2nd	15	—	1	—	—	

[a] The first blood sample was drawn immediately before .accination and the second at the end of the observation period (21-30 days later).

[b] In all instances where a child's serum was positive in both the first and second samples, it was positive to the same titre in both samples.

general reaction in a relatively high proportion of persons. However, no accidents or serious complications due to the vaccine were observed in this trial.

The combination of gamma-globulin with the vaccine did not greatly reduce either the percentage or the intensity of the reactions. In view of this and of the fact that the administration of gamma-globulin renders the vaccination procedure more complicated, the use of vaccine alone would seem preferable in any national mass-vaccination programme. In a country such as Chile, where measles is a serious disease involving a high mortality, such objections as might be raised to the use of the vaccine on account of the reactions it gives rise to would seem to be of relatively little weight.

As the general reactions regularly appear on about the fifth day after vaccination, the use of antipyretics in small doses for two or three days would help to attenuate the fever.

A vaccination programme should not be designed as a widespread campaign for immunizing most of the susceptible population over a short time as this would concentrate the case load at clinics on account of the reactions to vaccination and would thus unjustly give the method a bad reputation. We also believe that, in order to avoid undue worry or alarm among parents or physicians, vaccination should be performed under the strictest supervision and control.

From the experience we have obtained, we conclude that vaccination may usefully be carried out in Chile among all children from eight months to three years of age, and more particularly among the poor and the undernourished, preference being given to the central and southern regions of the country where the mortality from measles is highest.

The development of a vaccine giving fewer general reactions would be very valuable as such a vaccine would be much more readily accepted by both the public and physicians.

Consideration should also be given to vaccination with killed virus followed by administration of live virus in order to reduce the reactions to the latter.

Finally, mention should be made of the fact that in May 1963 the Chilean National Health Service started vaccination of a large number of children with the Enders Edmonston B vaccine in order to reduce the high measles mortality in the country. The conditions mentioned above have, of course,

been taken into account. For this purpose, 50 000 doses of vaccine have been kindly provided by the Merck Institute for Therapeutic Research, West Point, Pa., USA.

So far, more than 15 000 children in different cities have been vaccinated. There has been only one accident attributable to the vaccine—a mild case of encephalitis which occurred 10 days after vaccination; the patient has fully recovered. This accident is still being investigated.

The results of this large-scale vaccination programme will be published later.

RÉSUMÉ

En 1960, les décès par rougeole ont représenté plus de la moitié des décès par maladies infectieuses au Chili; leur nombre s'est élevé à 2116, la plupart étant des enfants de moins de 4 ans, appartenant aux classes les moins favorisées de la population.

Un essai de protection par le vaccin atténué Enders, préparé à partir de la souche Edmonston B, était particulièrement justifié, dans le cadre des études de vaccination contre la rougeole effectuées sous les auspices de l'OMS. A cet effet, on a formé cinq groupes de 100 enfants sensibles chacun, ayant de 8 mois à 3 ans. Le premier groupe a reçu le vaccin seul, trois autres ont reçu le vaccin et des quantités décroissantes de gammaglobuline, le cinquième, servant de témoin, reçut un placebo.

Un échantillon de sérum a été prélevé avant la vaccination et 28-32 jours après. Au cours de la période postvaccinale, les enfants ont présenté une fièvre modérée, et, en proportions variables, du rash, de la conjonctivite, de la diarrhée, etc. Quelques-uns d'entre eux seulement eurent des réactions plus graves.

Le titrage des anticorps fixateurs du complément, effectué à l'Institut de Bactériologie du Chili, révéla la présence d'anticorps spécifiques chez plus de 90% des enfants, ce qui correspond au pourcentage obtenu dans d'autres pays.

A la suite de ces résultats, et en raison de la gravité de la rougeole au Chili, une campagne massive de vaccination par vaccin atténué qui a touché plus de 15 000 enfants a été entreprise en 1963.

REFERENCES

Chile, Servicio Nacional de Salud (1961) *Enfermedades infecciosas de declaración obligatoria e inmunizaciones, 1961*, Santiago

Enders, J. F., Katz, S. L. & Holloway, A. (1962) *Amer. J. Dis. Child.*, **103**, 335-340

Fadeeva, L. L., Dadashyan, M. A., Lebedev, D. D. & Zhdanov, V. M. (1962) *Amer. J. Dis. Child.*, **103**, 379-381

Hilleman, M. R., Buynak, E. N., Weibel, R., Halenda, R. & Goldner, H. (1962) *Amer. J. publ. Hlth*, **52**, Suppl., pp. 44-56

Hilleman, M. R., Stokes, J., Jr, Buynak, E. N., Weibel, R., Halenda, R. & Goldner, H. (1962) *Amer. J. Dis. Child.*, **103**, 372-379

Ristori, C., Boccardo, H., Borgoño, J. M. & Armijo, R. (1962) *Amer. J. Dis. Child.*, **103**, 236-241